UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,956	09/20/2007	Edward H. Cohen	C007-7022US0	2118

56679 7590 03/02/2010

GOSZ AND PARTNERS LLP
ONE STATE STREET
BOSTON, MA 02109

EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	
MAIL DATE	**DELIVERY MODE**
03/02/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,956	COHEN ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *12-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 12/23/2009, is acknowledged.

2. Claims 1-33 are pending.

3. Claims 12-33 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

4. Claims 1-11 are under examination as they read on a protein comprising HC and LC that binds to an activated conformation of LFA- 1.

5. For clarity reasons, it is suggested that the preamble of the claims be change to "An isolated antibody" instead of "A protein".

6. The following new ground of rejections are necessitated by the amendment submitted 12/23/2009.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) The recitation "the heavy chain variable domain comprises a sequence encoded by a nucleic acid that hybridizes under high stringent conditions to a sequence that encodes the heavy chain variable domain SEQ ID NO: 42, SEQ ID NO: 43 or SEQ ID NO: 44;" in claim 1 (v) is indefinite and ambiguous. First, it is noted that SEQ ID NOs: 42-44 are nucleic acid sequences not protein sequences, it is known that nucleic acid sequence encodes protein sequence. In the instant case, it is unclear how nucleic acids would encode a nucleic acid sequence. Second, nucleic acid hybridization is a process by which the DNA of a gene is detected by its base pairing with a **complementary** sequence on another nucleic acid molecule. In the instant case, since the nucleic acid hybridizes to a sequence that encodes the heavy chain variable domain, the resultant sequence must be a complementary sequence, it is not clear how the complement sequence (antisense) would encode the claimed heavy chain variable domain.

B) The recitation "the light chain variable domain comprises a sequence encoded by a nucleic acid that hybridizes under high stringent conditions to a sequence that encodes **the light chain variable domain sequence** of SEQ ID NO: 42, SEQ ID NO:43, SEQ ID NO:44 antibody" is indefinite and ambiguous. In addition to having the same issue under section (A) above, the recited sequences (SEQ ID NOs: 42-44) encodes HEAVY variable domain not LIGHT variable domain.

C) Claim 4 stands indefinite in the recitation of " P1-G10" because its characteristics are not known. The use of "P1-G10" Fab antibody as the sole means of identifying the claimed antibody renders the claim indefinite because "P1-G10" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designations to define completely distinct clone. It is suggested that a deposit number be cited in the claims.

9. In view of the amendment filed on 12/23/2009only the following rejections are remained.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 4 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the cell line that produces the anti-activated LFA-1 Fabs, **P1-G10** is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the cell line, which produces this antibody, may satisfy first paragraph. See 37 CFR 1.801-1.809 for the same reasons set forth in the previous Office Action mailed 09/25/2009.

Applicant's arguments, filed 01/20/2010, have been fully considered, but have not been found convincing.

Applicant submits that the amended claims are no longer recite the antibody P1-G10 by name, but in the present particular sequences.

However, claim 4, still recite the antibody by name.

12. Claims 1-11 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 09/25/2009.

Applicant is in possession of an anti-activated LFA-1 antibody comprising VH and/or VL of SEQ ID NOS: 34/33, 36/35, 38/37 or 61/60 (listed on page 85-86 of the specification); or an

anti-activated LFA-1 antibody comprising VH CDR1-3 of SEQ ID NOS: 1-3 and VL CDR1-3 of SEQ ID NOs:7-9.

Applicant is not in possession of the protein claimed in claims 1-11.

Applicant's arguments, filed 01/20/2010, have been fully considered, but have not been found convincing.

Applicant submits that the claims have now been amended in order to claim more specific embodiments of the invention as described with more particularity in the present Sequence Listing. In view of these amendments, the claims are now believed to be in full compliance with the written description requirement, and to otherwise overcome this rejection.

However, the term "and/or" in claim 1(i) and 1(ii) reads on an antibody that comprises only a single CDR. Furthermore, the term "the heavy/light chain variable domain comprises" in claim 1(i)/claim 1(ii) reads on CDR1-3 without the knowledge of the antibody framework, which plays a role in the antibody binding. Furthermore, the recitation "at least the CDR regions of (i) and (ii) in claim 2 reads at least two CDRs and up to six CDRs.

The previous Office Action states:
The specification provides four anti-activated LFA-1 antibody which was not random combinations of VH and VL i.e., it had specific VH domain (SEQ ID NO: 36-38 and 61) paired with specific VL domain (SEQ ID NO: 33-35 and 60). No other VH domain was provided that share the less than the full length of all CDR1-3 of SEQ ID NO: 1-3 or the full length of all VL CDR1-3 of SEQ ID ON:7-9. The state of the prior art (see e.g. Klimka et al., British Journal of Cancer (2000) 83:252-260, and Beiboer et al., J. Mol., Biol. (2000) 296:833-849) is that methods for screening rely on a two step process where each step results in an antibody. However, each step requires one of the variable domains to be a defined sequence and the defined variable domain provides enough structure to obtain an antibody. The prior art methods do not result in an antibody solely by keeping only one CDR in the VH/VL defined and randomized the rest of the VH and VL domains. The prior art indicated that, in some instances, the CDR3 region is important. However, this region is not solely responsible for binding. The conformation of the other CDRs, as well as framework residues influence binding.

However, neither the specification, nor the prior art provides any examples to support the premise that only one CDR of the VH or VL is solely responsible for antigen binding. The prior art does not support a definition of an antibody structure solely by defining the CDR sequence of a VH or VL. Accordingly, the disclosed species would not be deemed by one of skill in the art to be representative of the claim scope. The claims do not meet the requirement s of 35 USC 112, first paragraph for written description.

13. Claims 1-11 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an anti-activated LFA-1 antibody comprising VH and/or VL of SEQ ID NOS: 34/33, 36/35, 38/37 or 61/60 (listed on page 85-86 of the specification); or an anti-activated LFA-1 antibody comprising VH CDR1-3 of SEQ ID NOS: 1-3 and VL CDR1-3 of SEQ ID NOs:7-9, does not reasonably provide enablement for the protein claimed in claims 1-11. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action mailed 09/25/2009.

Further, the recitation "a nucleic acid that hybridizes … to **a** sequence" claim 1(v-vi) reads on fragments because this recitation encompasses nucleic acids that comprise the full-length sequence of SEQ ID NO: 42-44 or any portion of SEQ ID NO: 42-44. It is suggested that the claim be changed to "the sequence" to overcome the rejection.

Applicant's arguments, filed 01/20/2010, have been fully considered, but have not been found convincing.

Applicant submits that the claims have now been amended in order to specify with greater particularity the scope of the invention.

However, the Applicant is still claiming an antibody that binds to an activated conformation of LFA-1 comprising a single CDR. It is noted that claim 1(i-ii) still recites the term "and/or". Furthermore, claim 1(i-ii) still recites the claimed antibody with any VH or VL comprising only 3 CDRs without specifying the framework of the VH or VL. The previous Office Action states:

With respect to making the genus of anti-activated LAF-1 antibodies using a set of particular VH CDRs and/or VL CDRs as the starting point, e.g., SEQ ID NOs: 1-3 and/or CDR 7-9 as recited in claim 1, it is known in the art that antibody-antigen affinity and specificity is a function of not only direct CDR to antigen interactions, but also the interactions of the CDRs with framework residues in the same chain, e.g., VH CDR binding to VH framework residues, and in the opposing chain, e.g., VH CDR binding to VL framework residues. In addition, the CDR residues of each chain can interact with the CDRs of the opposite chain. It is for this reason that antibody humanization protocols, e.g., humanization of a murine antibody, provide extensive guidelines as to the retention of certain murine residues in the context of the human framework so as to preserve this web of interactions, the loss of any one of these interactions having the potential to ablate antibody-antigen binding (see, e.g., Eduardo Padlan, Mol Immunol. 1994 Feb;31(3):169-217, in particular column bridging paragraph on page 177; page bridging paragraph pages 178-179 through page 180; pages 201, 204 and Tables 8, 22 and 23 and Adair et al., United States Patent No. 5,859,205, in particular columns 1-6, 9-11 and 27-28).

Regarding claim 5, the previous Office Action states:

Claim 5 recite that the protein binds activated LFA-1 has the heavy chain variable domains sequence comprises Xa-S-X2-D-X4-X5-S-X7-A-X8-X9-X10-X11 of SEQ ID NO: 4. However, the highly diverse VH CDR3 loops are the key determinant of specificity in antigen recognition in antibodies, and may allow the isolation of a new specificity. However, the specification fails to show which of the claimed amino acid or their combination would lead to a binding to activated LFA-1 protein. Given that the claimed antibody recognizes a conformational activated LFA-1 protein, the predictability of which amino acid or their combination that would lead to an antibody that would bind to the claimed activated LFA-1. Changes in the CDR3 sequence of the VH would deviate from the original antigen reactivity and specificity.

Regarding claim 11, the previous Office Action states:

At issue is whether the claimed protein that binds activated LFA-1 would function as a pharmaceutical composition (intended use) in claim 11. The exemplification is drawn to the use of D2-57 to bind HA cells (cells expressing an

LFA-1 with an I-domain locked in the high affinity conformation) relative to LA cells (cells expressing an LFA-1 with an I-domain locked in the low affinity conformation) (see Fig. 1 in particular). In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the pharmaceutical composition as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed pharmaceutical composition are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1, 3, 6-11 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/23761 A1 as is evidenced by the specification on page 84, lines 1-7 for the same reasons set forth in the previous Office Action mailed 09/25/2009.

Applicant's arguments, filed 01/20/2010, have been fully considered, but have not been found convincing.

Applicant submits that the present claims have been amended and no longer correspond to the amino cid sequences described in the Office Action.

However, the reference antibodies would still "compete" with the claims antibodies recited in claim 1(vii) and would and read on the claimed antibodies claimed in claim 10 in the absence of evidence to the contrary. Further, given the high sequence homology between the referenced/claimed antibody heavy/light variable domains; the referenced nucleic acid encoding the reference antibodies would have hybridize to the claimed sequence and bind the to activated LFA-1. In the absence of recitation that the hybridization is over the full length of SEQ ID NO:42-44, the prior are reads on the claimed antibodies. Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody does not compete with the antibody recited in the claim or does not have the claimed IC50 recited in claim 10. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

13. Claims 1 and 6-11 are rejected under 35 U.S.C. 102(b) as being anticipated by US 2002/0123614 A1 (of record) for the same reasons set forth in the previous Office Action mailed 09/25/2009.

Applicant's arguments, filed 01/20/2010, have been fully considered, but have not been found convincing.

Applicant submits that Applicant that there is no evidence that the antibodies described in the reference contain the specific heavy chain and light chain variable domains required in the present claims. Any conclusion that the antibodies are equivalent can only be based on speculation without concrete evidence to support such a conclusion. The burden is on the USPTO in the first instance regarding equivalency, and applicant should not be required to prove a negative, i.e. that the present claims do not cover the antibodies of the reference. This conclusion is also supported by the observation that the present claims now exclude numerous antibodies which may or may not be described in the reference

However, the reference antibodies would still "compete" with the claims antibodies recited in claim 1(vii) and would and read on the claimed antibodies claimed in claim 10 in the absence of evidence to the contrary. Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody does not compete with the antibody recited in the claim or does not have the claimed IC50 recited in claim 10. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

14. No claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

February 26, 2010

/Maher M. Haddad/
Primary Examiner,
Art Unit 1644